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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER

STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 05/22/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/808,124

Applicant(s)

POTTER ET AL.

Examiner

Teresa E Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) 1(b),(c), 3-8, 10, 23, 24, 29-31, 33-46, 53-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1(a), 2, 9, 11, 13, 17, 18, 21, 25-28, 32, 47-52 is/are rejected.
- 7) ☒ Claim(s) 12,14-16,19,20 and 22 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8,9,13.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1(a), 2, 9 (all in part), 11-22, 25-28 (all in part), 32 and 47-52 (all in part), drawn to M-MLV reverse transcriptase) in Paper No. 12 is acknowledged. The traversal is on the ground(s) that 1) for the restriction to be proper the inventions must be independent or distinct and there must be a serious burden on the examiner if restriction is not required, and 2) Groups I-XLI (claims 1-46) are all drawn to reverse transcriptases, which are related, therefore these claims should be examined together.

This is not found persuasive because the independent claim 1 is drawn to a reverse transcriptase which has been modified or mutated by at least one way selected from the group consisting of : (a) increasing or enhancing fidelity, (b) reduction or elimination of nucleotide misincorporation and (c) decrease or elimination of terminal deoxynucleotidyl transferase. Therefore, claim 1 is drawn to seven different reverse transcriptase enzymes, with different amino acid sequences and functions. In addition, each of these modifications or mutations can be made to either MMLV, RSV or AMV reverse transcriptases, which are also different enzymes. In terms of claim examination burden, examining claim 1 with all the dependent claims would mean examining 21 different types of reverse transcriptases, and since their sequences and structures are not related, this would constitute a serious burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1(b) and (c), 3-8, 10, 23, 24, 29-31, 33-46 and 53-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement

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in Paper No. 9. Claims 1(a), 2, 9 (all in part), 11-22, 25-28 (all in part), 32 and 47-52 (all in part) will be examined as being drawn to the M-MLV reverse transcriptase.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1(a), 2, 9, 32 and 47-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an M-MLV reverse transcriptase (RT) with enhanced fidelity, reduced nucleotide misincorporation and decreased terminal deoxynucleotidyl transferase (TdT) activity, does not reasonably provide enablement for any other reverse transcriptase with such properties. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The following facts are presented in the specification: 1) M-MLV RT mutations Y64W, R116M, K152R, Q190F, T197A and V223H resulted in RTs with increased fidelity and lower degree of nucleotide misincorporation (Table 2, [0140], [0141]); 2) mutations F309N, T197E and Y133A resulted in RTs with decreased TdT activity ([0142], [0149]), and 3) mutations F309N and F309N/V223H had increased fidelity as well. The specification does not provide reasoning why these residues were chosen for making changes and how the choice of replacement amino acid was decided.

Due to the large quantity of experimentation necessary to determine all possible mutations in all possible reverse transcriptases which will result in increased enzyme fidelity, decreased nucleotide misincorporation and decreased TdT activity, or a combination of any

of these functional characteristics, the lack of direction and guidance presented in the specification regarding creation of all possible mutations in all possible reverse transcriptases which will result in increased enzyme fidelity, decreased nucleotide misincorporation and decreased TdT activity, or a combination of any of these functional characteristics, the absence of working examples directed to making such mutations in reverse transcriptases other than M-MLV RT, the unpredictability of the effects of mutations on protein structure and function (see references below), undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

In M-MLV RT, Val223 is a part of the conserved YXDD motif in reverse transcriptases and has been implicated in the fidelity of DNA synthesis. The conserved Tyr222 was mutated to Phe, Ser and Ala, but only Y-> F mutant had increased fidelity, whereas the Y-> S and Y-> A mutants had significantly reduced activity (Kaushik et al., Biochemistry, vol. 38, pp. 2617-2627, 1999). Glutamine 190 mutations to Asn and Ala had significantly reduced polymerase and pyrophosphorylase activities (Jin et al., J. Biol. Chem., vol. 274, pp. 20861-20868, 1999). Arg 110 replacements with Lys, Ala or Glu resulted in a loss of polymerase activity and no impairment of RNase H function (Chowdhury et al., Biochemistry, vol. 35, pp. 16610-16620, 1996). Halvas et al. (J. Virology, vol. 74, pp. 312-319, January 2000) describe an assay for determining fidelity of reverse transcriptases and testing the V223M, V223S, V223A, V223I and Y598V mutants of M-MLV RT using the assay. The V223M, V223S, V223A mutants had higher error rates than the non-mutated RT, and the V223I mutant had the same error rate.

5. Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the M-MLV RT with 1.5 to 2.3 decrease in mutation frequency, does not

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reasonably provide enablement for any reverse transcriptase mutated in such a way that its fidelity is increased 1.5 to 50-fold, 10 to 50-fold, 20 to 50-fold or 30 to 50-fold over the unmodified enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification provides an example of M-MLV RT with 1.5 to 2.3 decrease in mutation frequency with the Y64W, R116M, K152R, Q190F, T197A and V223H mutations ([0140]), but does not provide guidance of how to achieve higher fidelity than about 2.3 fold.

Due to the large quantity of experimentation necessary to determine all possible mutations in all possible reverse transcriptases which will result in increased enzyme fidelity up to 50-fold over the unmodified enzyme, the lack of direction and guidance presented in the specification regarding creation of all possible mutations in all possible reverse transcriptases which will result in increased enzyme fidelity up to 50-fold over the unmodified enzyme, the absence of working examples directed to making such mutations in reverse transcriptases other than M-MLV RT, the unpredictability of the effects of mutations on protein structure and function (see references above), undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 17 and 18 are drawn to a modified or mutated M-MLV reverse transcriptase with Glu190 replaced by phenylalanine. Residue 190 in M-MLV reverse transcriptase is a glutamine, Gln.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1 (a), 2, 9, 25, 47-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaushik et al. (Biochemistry, vol. 38, pp. 2617-2627, March 2, 1999).

Kaushik et al. teach a mutated MMIV RT in which the Tyr222 was mutated to Phe, Ser and Ala. The Phe substitution resulted in an enzyme with higher fidelity than the unmutated MMLV RT, by a factor of up to two-fold (Abstract; page 2622; page 2623, second paragraph; Fig. 3, 4). The mutated enzyme was produced by site-directed mutagenesis, cloned into pET-28a-MRT expression vector, expressed from E. coli BL-21 strain, isolated and purified (page 2618, paragraphs 5 and 6).

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 2, 9, 11, 13, 17, 21 and 47-52 provisionally rejected under the judicially created doctrine of double patenting over claims 16, 24-26, 28, 30-35 of copending Application No. 09/847,157. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both sets of claims are drawn to a reverse transcriptase which has increased fidelity and/or decreased terminal deoxynucleotidyl transferase (TdT) activity, the RT being MMLV RT, and the mutations resulting in increased fidelity are in residues Tyr64, Arg116, Gln190 or Val223.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

12. No references were found teaching or suggesting claims 11-22, 26-28 and 32. Claims 12, 14-16, 19, 20 and 22 are objected to as being dependent on the rejected claims 1, 9, 11, 13, 17, 18 and 21. Claims 11, 13, 17, 21, 26-28 and 32 are rejected for other reasons.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
May 14, 2002 TS.

Kenneth R. Horlick
KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
5/15/02